REMARKS

The claims have been amended for formal reasons and for consistency. Claim 1 has been amended to clarify the nature of the invention; the immunogenic composition is intended to elicit an immune response to the pathogenic organism of which the polysaccharide component is characteristic.

Claims 4-8 contain entirely formal amendments, as do claims 13-15. These claims are simply reworded forms of the prior claims; claim 14 is, however, equivalent to former claim 16.

Claim 19 has been amended for clarification and claims 20-35 are simply "cleaned up" versions of the claims previously pending.

Claim 36 is amended so as to depend from claim 1.

New claims 62-63 are added for completeness. New claims 64-66 are directed to methods to use the compositions already claimed. It is believed that the subject matter of new claims 64-66 is properly examined along with claims to the immunogenic composition.

No new matter has been added and entry of the amendment is respectfully requested.

Formal Matters

The objections to the claims have been met by the above amendment.

The Invention

The invention is directed to providing alternative immunogenic carriers for polysaccharide-based vaccines. One of the problems encountered in immunizing subjects for protection against infection where the antigen is a polysaccharide is that such polysaccharides may not be sufficiently immunogenic alone to elicit an immune response. Therefore, they require the use of an immunogenic carrier to aid in eliciting an immune response. Such carriers as pertussis toxin, diphtheria toxin, and tetanus toxin have been frequently used; however, overuse of these carriers results in the inability of the subject to later respond to administration of a vaccine for protection against these microorganisms. Thus, for example, if tetanus toxoid is used as a carrier, there is a possibility that the subject will no longer respond to immunization

against tetanus. Therefore, it is desirable to provide a variety of carriers in order to prevent overuse of a single type.

The present invention fills this need by providing proteins characteristic of *C. difficile* as alternative carriers. As described in the specification and demonstrated in the examples, these carriers are effective in causing an immune response to a co-administered polysaccharide.

The Rejections

Claims 1-19 and 36-39 were rejected as assertedly anticipated by Kink. It is believed this basis for rejection is in error. Kink, U.S. 5,736,139, fails to disclose all of the limitations of claim 1, the only independent claim currently pending. The compositions of Kink do not contain a polysaccharide from a pathogenic microorganism which is different from *C. difficile*. The compositions of Kink contain only *C. difficile* toxin proteins and are intended to elicit responses to produce antitoxins which then can be used to neutralize *C. difficile* toxins *per se*. They contain no combination of these *C. difficile* toxins with polysaccharides characteristic of other microorganisms. Accordingly, the rejection for anticipation by Kink may properly be withdrawn.

Claims 1-19 and 36-39 were rejected as assertedly anticipated by Thomas, *et al.* Thomas discloses *C. difficile* toxins as mucosal adjuvants, but does not suggest the use of these adjuvants to elicit responses to polysaccharide antigens. The only antigens described in Thomas are, themselves, proteins. Thus, not only does Thomas fail to disclose the use of *C. difficile* toxins as adjuvants for polysaccharides, Thomas teaches away from this by suggesting that the adjuvant activity of *C. difficile* is limited to protein antigens. In any event, Thomas cannot anticipate, because Thomas fails to disclose all of the elements required by the claims. Accordingly, this basis for rejection may also be withdrawn.

Claims 1-19 and 36-39 were rejected as assertedly anticipated by Williams. Williams is issued on an application which is a parent to the application which issued as the Kink patent. Williams fails to disclose all of the elements of claim 1 since there is no disclosure of combining, in an immunogenic composition, the product of a *C. difficile* gene with a polysaccharide antigen. Like Kink, Williams is concerned with providing a composition which elicits the production of

antibodies to type A toxin proteins. There is no mention of using *C. difficile* proteins in combination with polysaccharides in compositions to elicit an immune response to the pathogenic microorganism characterized by the polysaccharide. Accordingly, this basis for rejection may also be withdrawn.

The rejections under 35 U.S.C. § 103 all depend ultimately on Kink, *et al.*, as a primary reference. This dependence assumes that Kink discloses the use of *C. difficile* toxins in combination with polysaccharides in general in compositions to elicit immune responses to microorganisms characterized by the polysaccharide. However, as noted above, Kink does not in fact disclose this. Kink, instead, discloses only the use of *C. difficile* toxin A itself to elicit antibodies immunoreactive with the toxin A itself which are designed to neutralize the toxin. Therefore, for this reason alone, all rejections based ultimately on Kink may be withdrawn. Kink does not provide the generic teaching which would be required to support these rejections.

For completeness, the following comments are offered.

Claims 20-24 were rejected as assertedly obvious over the combination of Kink with Schneerson, *et al.* Schneerson, *et al.*, is cited as disclosing a *Streptococcus pneumoniae* capsular polysaccharide coupled with pertussis toxin as an immunogenic carrier. However, the combination of Schneerson with Kink fails to suggest the claimed invention, even if there were motivation to combine these documents. Kink fails to suggest the use of *C. difficile* proteins as immunogenic carriers with regard to any polysaccharides or, indeed, with respect to any antigens at all to which an immune response is desired. Thus, the combination of Schneerson with Kink, even if made, fails to suggest the present invention.

In addition, there is no motivation to combine these documents. As set forth by the Federal Circuit in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), it is incumbent on the Office, when combining documents, to provide a rationale for motivation to combine them. No such rationale has been provided in this case. The basis for rejection is entirely silent on such motivation. Indeed, no such motivation is apparent to applicants. Accordingly, this basis for rejection may be withdrawn.

Claim 25-26 were rejected as assertedly obvious over Kink in combination with Schneerson and in further view of Taylor, *et al.* Taylor is cited as disclosing polysaccharides of *Shigella* which are the subject of claims 25 and 26. It is unclear what the relevance of Schneerson might be in the context of this rejection. In any event, the cited combination fails to defeat patentability of claims 25-26 for reasons similar to those set forth above with regard to claims 20-24. The combination of these three documents fails to suggest the invention as claimed since Kink does not suggest the use of *C. difficile* toxins as immunogenic carriers for polysaccharides in general. Similar to Schneerson, Taylor merely suggests coupling *Shigella* polysaccharides to different bacterial toxoids, not *C. difficile*. Any suggestion to substitute *C. difficile* for the toxoids described in Taylor is nowhere to be found. And once again, there is no rationale provided for why one would combine the teachings of Schneerson, Kink, and Taylor, as would be required to support such a combination rejection.

Claims 27-31 were rejected as assertedly obvious over the combination of Kink, Schneerson, Taylor and Devi. Devi is added because it describes conjugates of *Escherichia coli* and *Meningococci* polysaccharides. *Neisseria* and *E. coli* polysaccharides are subjects of these claims. Again, it is difficult to see the relevance of Schneerson and Taylor with regard to this rejection; they relate to organisms not set forth in claims 27-31. The combination of Kink and Devi also fails to suggest the claimed invention for the reasons set forth above; there is no suggestion in either document that *C. difficile* be used as an immunogenic carrier for any polysaccharide. And once again, no motivation for the combination is provided.

Finally, claims 31-35 were rejected as assertedly obvious over Kink, Schneerson, Taylor, Devi and Fattom. Fattom is cited with regard to these claims because these claims include *Staphylococcus aureus* as the pathogenic organism characterized by the polysaccharide component. Schneerson, Taylor and Devi appear entirely irrelevant; Kink has the deficiencies set forth above, and the combination of Kink with Fattom fails to suggest the invention because no document suggests the use of *C. difficile* as an immunogenic carrier to enhance an immune response against a polysaccharide. And again, no rationale is provided for a motivation to combine these documents. This basis for rejection also may be withdrawn.

CONCLUSION

The claims have been amended for good order. Claim 1 has been amended to clarify that it is an immunogenic response against the pathogenic microorganism, of which the polysaccharide is characteristic, that is elicited by the composition. The presence of *C. difficile* toxin enhances the strength of this response.

It has been demonstrated that neither Kink nor Williams envision the use of *C. difficile* proteins to enhance the immune response to any other antigen, much less to polysaccharides. Thomas suggests only the use of *C. difficile* toxin A as an adjuvant to mucosal vaccines for responses against peptide or protein antigens. The secondary references merely describe alternate conjugates with polysaccharides and fail to suggest the use of *C. difficile* proteins for this purpose. Further, there is no motivation shown to combine any of the secondary references with Kink as is necessary to support the rejections made under § 103. Accordingly, it is believed that the pending claims, claims 1-8, 13-15, 19-20, 23-26, 28-31, 33, 36-39 and 62-66 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 420522000100.

Respectfully submitted,

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Amended) An immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises [comprising] a recombinant protein and a polysaccharide component, wherein said protein is encoded by a gene from a strain of *Clostridium difficile* and said polysaccharide component is [isolated from a strain of] characteristic of a pathogenic microorganism [or chemically synthesized] , which pathogenic microorganism is other than *C. difficile*.

4. (Amended) The immunogenic composition of claim [1] 2, wherein said [protein] toxin is toxin A or a fragment thereof.

5. (Amended) The immunogenic composition of claim 4, wherein said [protein] toxin comprises a recombinant amino acid sequence that includes the toxin A repeating units (*r*ARU) or a fragment thereof.

6. (Amended) The immunogenic composition of claim [5] 1, wherein said protein is a fusion protein.

7. (Amended) The [immonogenic] immunogenic composition of claim 1, wherein said protein is toxin B or a fragment [threreof] thereof.

8. (Amended) The immunogenic [composistion] composition of claim 7, wherein said [protein] toxin comprises a recombinant amino acid sequence that includes the toxin B repeating units (*r*BRU) or a fragment thereof.

13. (Amended) The immunogenic composition of claim [10 or 11 or 12] 1, wherein said immune response [is] comprises a cellular [dependent] immune response.

14. (Amended) The immunogenic composition of claim [10 or 11 or 12] 1, wherein said immune response [results in a booster effect in said mammalian host] comprises an immune response.

15. (Amended) The immunogenic composition of claim [10 or 11 or 12] 1, wherein said immune response [elicits a] is protective [response to a strain of] against said pathogenic microorganism.

19. (Amended) The immunogenic composition of claim [18] 1, wherein said [strain of a pathogenic microorganism produces said] polysaccharide [*in vivo*] has been isolated from said pathogenic microorganism.

20. (Amended) The immunogenic composition of claim [19] 1, wherein said [polysaccharide is isolated from a strain of a] pathogenic microorganism is selected from the group consisting of [strains of]: *Streptococcus pneumoniae*; *Neisseria meningitidis*; *Escherichia coli*; and *Shigella*.

23. (Amended) The immunogenic composition of claim [19] 20, wherein said [polysaccharide is isolated from serotype 14 of] pathogenic microorganism is *Streptococcus pneumoniae*.

24. (Amended) The immunogenic composition of claim [18] 23, wherein said immune response [elicits a] is protective [response to a strain of] against *Streptococcus pneumoniae*.

25. (Amended) The immunogenic composition of claim [18] 20, wherein said [polysaccharide is isolated from a strain of] pathogenic microorganism is *Shigella*[*flexneri*, serotype 2a].

26. (Amended) The immunogenic composition of claim [18] 25, wherein said immune response [elicits a] is protective [response to a strain of] against *Shigella*.

28. (Amended) The immunogenic composition of claim [19] 20, wherein said pathogenic microorganism is [group B meningococcus (]*Neisseria meningitidis*[serogroup B)].

29. (Amended) The immunogenic composition of claim [19] 20, wherein said pathogenic microorganism is *Escherichia coli* K1.

30. (Amended) The immunogenic composition of claim [19] 1, wherein said [polysaccharide] pathogenic microorganism is selected from the group consisting of: *Staphylococcus aureus*; coagulase-negative *Staphylococcus*; *Enterococcus* species; *Enterobacter* species; *Candida* species; [group B *Streptococcus; Escherichia coli*;] and *Pseudomonas* species.

31. (Amended) The immunogenic composition of claim [19] 30, wherein said immune response [elicits a] is protective [response to a strain of a nosocomial pathogenic microorganism selected from the group consisting of strains of:] with respect to *Staphylococcus aureus*; coagulase-negative *Staphylococcus*; *Enterococcus* species; *Enterobacter* species; *Candida* species; [group B *Streptococcus; Escherichia coli;* and] or *Pseudomonas* species.

33. (Amended) The immunogenic composition of claim [19] 30, wherein said pathogenic microorganism is *Staphylococcus aureus* serogroup 5 or serogroup 8.

36. (Amended) [An] The immunogenic composition of claim 1 which [comprising a recombinant protein and a polysaccharide component, wherein said protein is encoded by a gene isolated from a strain of *Clostridium difficile* and said polysaccharide is a polysaccharide isolated from a strain of a pathogenic microorganism or chemically synthesized and wherein said composition] further comprises a pharmaceutically acceptable carrier.